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ROLE OF PAP SMEAR TO DETECT CYTOLOGICAL ABNORMALITIES IN CERVICAL LESIONS IN TERTIARY CARE HOSPITAL

Dr. NAMRATA

Deemed to be Santosh University

No.1, Santosh Nagar,

Ghaziabad - 201009, NCR, India.

DEPARMENT OF PATHOLOGY

SANTOSH MEDICAL COLLEGE AND HOSPITAL

GHAZIABAD NCR, DELHI

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Guide

Dr. PREM K GARG MD
Designation-Professor & HOD
Department of pathology
Saraswathi Institute of Medical Sciences
Hapur (U.P.), India.

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This is to certify that the thesis titled **"ROLE OF PAP SMEAR TO DETECT CYTOLOGICAL ABNORMALITIES IN CERVICAL LESIONS IN TERTIARY CARE HOSPITAL"**will be bonafide genuine research work carried out by **Dr. NAMRATA** in partial fulfilment of the requirements for award of the degree of M.D. in the speciality of PATHOLOGY.

Co-Guide

Dr. ABHISHEK PATHRE, MD
Designation-AssistantProfessor
Department of Pathology
Santosh Medical College & Hospital
Ghaziabad (UP), India.

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This is to certify that the thesis titled **"ROLE OF PAP SMEAR TO DETECT CYTOLOGICAL ABNORMALITIES IN CERVICAL LESIONS INTERTIARY CARE HOSPITAL"**will be bonafide research work carried out by **Dr. NAMRATA** in partial fulfilment of the requirements for award of the degree of M.D. PATHOLOGY will be based on bonafide work carried out by her under my guidance and supervision and is completed to my full satisfaction.

PROF. (Dr.) RAJIVGUPTA, M.B.B.S., M.D.

Designation-Professor & HOD
Department of Pathology
Santosh Medical College & Hospital
Ghaziabad – 201001 (U.P)

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Dr ALKA AGRAWAL

Designation-Dean
Faculty of Medical Sciences
Santosh Medical College & Hospital
Santosh University
Ghaziabad – 201001 (U.P)

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LIST OF ABBREVIATION

ACOG	-	American College of Obstetricians and Gynecologists
ACS	-	American Cancer Society
AGC	-	Atypical glandular cells
AIS	-	Adenocarcinoma in situ
ASC	-	Atypical squamous cells
ASC-H	-	Atypical squamous cells cannot exclude an HSIL
ASC-US	-	Atypical squamous cells of undetermined significance
CAP	-	College of American Pathologists
CIN	-	Cervical intraepithelial neoplasia
CMV	-	Cytomegalovirus
CP	-	Conventional preparation
EC/TZ	-	Endocervical/transformation zone
FDA	-	Food and Drug Administration
Hpf	-	High–power field
HPV	-	Human papilloma Virus
HrHPV	-	High–risk human papilloma Virus
HSIL	-	High–grade squamous intraepithelial lesions
IUD	-	Intrauterine contraceptive device
LBP	-	Liquid–based preparation
LEEP	-	Loop electrosurgical excision

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INTRODUCTION

Cervical cancer is one of the most common cause death of women in developing countries[(1)].The numbers of new cases of cervical cancer according to National cancer registry of India is 90708 with 48% survival rate in 5 years[(2)]. Per year increase in new cases of India is 1,26,000[[3]]**.** It is easily preventable by effective programmes for detection and treatment of precursor lesions. Due to introduction of Pap smear, there is dramatic reduction in incidence and mortality of invasive carcinoma cervix in the world[[4]]

Pap smear is a cervical screening technique which has reduced death due to cervical cancer. Vaginal discharge, post-coital bleeding, intermenstrual bleeding, dyspareunia, pain lower abdomen are some of the complains of patients whose Pap smears were prepared

Non-specific inflammation such as Gardnerella infection Atypical Squamous Cell of Undetermined Significance[ASCUS] are inflammatory lesions in majority of cases. Low Grade Squamous Intra epithelial Lesion [LSIL] and High Grade Squamous Intraepithelial Lesion [HSIL] are also reported. Inadequate smears are also present.

Worldwide cervical cancer is second most common cancer in women. It is leading cause of cancer in developing world. Globally cervical cancer is 15% of total cancer in female[(3)]. But in south East Asia, cervical cancer is 20-30% of all cancers of female. In developing world cervical cancer is one of most common cause.

Over last decade, in developing countries the impact of cervical cytology screening due to invasive cervical cancer has been reduced the incidence and mortality. In developed countries, mortality due to cervical cancer has been decreased 70 – 80% in past 60 years. The incidence rate was 32/100,000in 1940 and 8.5/100,000 in 1980[(4)].

Cervical premalignant and malignant lesions are effectively screened by Papanicolaou [Pap] smear for cervical cytology. Important health problem in women worldwide is cervical intraepithelial neoplasia and cervical cancer. Most cervical cancer can be diagnosed at preinvasive stage with adequate and repetitive cytological screening. The study of different methods for the early detection of cervical abnormalities, correlation of clinical finding and

comparison between the techniques was carried out keeping in view of the carcinoma and precancerous lesions of cervix [CIN][5].

Adherence to Pap testing in HIV- positive female who smoke, is not well known. So HIV-positive women are at elevated risk of developing cervical carcinoma. HIV- positive women don't utilise gynaecological health care facilities as research suggest. A baseline data from a smoking cessation trial suggested that younger age, African American race, hazardous drinking, increased no. of cigarette smoked per day was severely underutilised by women in the study and it is associated with non-adherence to Pap smear screening. Non- adherence and addressing multiple risk factors and behavioural pattern among HIV- positive women who smoke, are underscored.

Effective programmes are conducted to detect and treat precursor lesions of cancer cervix as it is readily preventable. A dramatic reduction has been observed in incidence and mortality of invasive cancer cervix worldwide due to introduction of Pap smear.

To meet both test and disease criteria for screening, cervical cancer is considered to be an ideal gynaecological malignanies[7]. Identifiable and treatable premalignant lesion which precede the invasive disease has a long latent phase during which it can be detected.

Premalignant and malignant lesions of cervix are not uncommon, while reviewing all results, it can be concluded. To detect premalignant and malignant lesions of cervix at an early stage, Pap smear for cervical cytology is done. It is simple safe and effective test and thus help the clinicians in early and more efficient management of the patient.

From patient relevant history of illness was obtained and recorded on proforma. On day of test, no local douche, antiseptic cream and no local internal examination was done, it was insured. A Cusco's bivalve speculum was introduced through vagina and cervix was visualized, when patient was placed in dorsal lithotomy position. Near squamo- columnar junction in the cervix, longer projection of the Ayre's spatula was placed and rotated through 360. On clean glass slide smear was prepared from the cellular material quickly. In the coplin jar containing 95% ethyl alcohol, glass slide was immediately put in ethyl alcohol act as fixative. According to Papanicolaou technique, the prepared smear where stained. According to new 2001 Bethesda system, the cytological interpretation of smear was made. 18.5 years,

19.5 years and 18.3 years where the mean age at marriage for patient with LSIL, HSIL and invasive carcinoma.

Vaginal discharge following post-menopausal bleeding was the most common presenting complaint associated with SIL and carcinoma[8]. Erosion followed by cervical bleeding on touch was the most common clinical reason seen in patient with SIL and cancer.

32.3 years was the main age of patient with LSIL and 40.5 years and 57 years respectively where the mean age of patient with HSIL and invasive carcinoma with increasing age, progressive increase in development of LSIL to invasive CA was recorded.

20 years was peak incidence of LSIL, 30-39 years for HSIL and 50-59 years was peak incidence for invasive cancer[8]. Patient to started sexual activity before 20 years of age LSIL and HSIL on cytology was more prevalent. Significance of vaginal discharge associated with neoplastic changes in cervix was emphasized in present study.

AIMS AND OBJECTIVES

The proposed study entitled **"ROLE OF PAP SMEAR TO DETECT CYTOLOGICAL ABNORMALITIES IN CERVICAL LESIONS IN TERTIARY CARE HOSPITAL"** was carried out with following objectives:

1. To study etiological factors of cervical lesions.
2. To analyse the utility and diagnostic importance of pap smear in cervical lesions.
3. To differentiate cervical premalignant lesion from malignant lesion.
4. To correlate Pap smears findings with histopathology whenever possible

REVIEW OF LITERATURE

Pap smearby cervical cytology is safe, simple and effective to detect cervical lesions early stage and help clinicians in early and more effective management of abnormalities of cervix worldwide[9].

To reduce cervical cancer rate dramatically, Papanicolaou [Pap] smear, cervical cytology screening has helped. It was implemented in 1950. There is evolution of Pap reporting classification[10]. Bethesda System has been refined with current standard. A large and complex clinical and public challenge is management of equivocal Pap test abnormality.

Cervical smear is diagnosed in 1, 22,844 Indian women every year. Death of 67,477 Indian women occur every year. In women of age 15-44 years, cervical cancer is 2nd most common cancer[11]. In south Asia, India also has the highest age of standardised incidence of cancer cervix.

To diagnose cervical vaginal precancerous and cancerous lesions, Pap smear test is simple, non-invasive cost effective. Most common epithelial cell abnormalities was ASCUS[12]. For both national and expatriate women, community health education and opportunistic screening for cervical cancer are recommended. An effective means of screening for cervical premalignant and malignant conditions are regional cervical cytology by Papanicolaou [Pap] smear[13].

Cervical carcinoma is presented by spectrum of intraepithelial neoplastic changes and does not develop suddenly from normal epithelium[14]. It is the precancerous lesion and termed as cervical intraepithelial neoplasia. Over 90% of cytological abnormality is designed to detect by cervical cytological screening[15].

With adequate and repetitive cytological screening, it is established that most cervical cancer can be diagnosed at the preinvasive stage[16]. Study of different methods for the early detection of abnormalities in cervix and correlation with the clinical finding and comparison between the technique was carried out by keeping in view of the important of carcinoma and precancerous lesion [CIN] of cervix[17].

To triage, women with minor cytological cervical lesions, Human papilloma virus [HPV] testing and repeat cytology are done. Who need referral for diagnostic explanation with colposcopy and biopsy, women are identified by triage[18].

By early detection and appropriate treatment of its precursor lesions by simple Pap smear, cancer of cervix is readily preventable[19]. When women have symptoms such as pain, discharge and abnormal bleeding, they usually present to clinic.

There is spectrum of intraepithelial lesions that lie along the pathway from mild to severe dysplasia to invasive carcinoma[20]. Overall sensitivity in detection of detection of high grade squamous intra- epithelial lesion [HSIL] is 70-80%, though Pap smear is routine screening test[21]. To provide clear guidance for clinical management, the Bethesda system for reporting the result of cervical cytology was developed as a uniform system of terminology[22].

Cervical intra-epithelia [CIN] is Human Papilloma virus related premalignant condition, histologically diagnosed, characterised by dysplastic changes in cervical epithelium, without stromal invasion[23]. The persistent high risk HPV infection is considered the necessary condition for the development of CIN[24]. Multiple sexual partner, and early stage at sexual debut, smoking and immune suppression, increasing the likelihood of cervical dysplasia, a previous hysterectomy for HPV related cervical lesion and presence of previous synchronous cervical dysplastic lesion, are believed to be associated to the development of CIN[25].

Single most important quality assurance component of Bethesda system is evaluation of specimen adequacy[26]. Three category of adequacy was included by first two version of the Bethesda terminology.'' Satisfactory, unsatisfactory and a borderline'' category initially termed as ''less than optimal'' and then renamed as ''satisfactory but limited by'' in 1991[27].Due to confusion among clinician in 2001 Bethesda system eliminated the borderline category.

Criteria used to report' 'satisfactory but limited by'' among laboratories due to appropriate follow-up for such finding[27]. Now specimen are designated as either ''satisfactory or unsatisfactory'' prior to the 2001 Bethesda system.

Entirely the expert opinion and the few available studies in the literature were the criteria for determining adequacy[28]. It was difficult to implement some of lab criteria[28]. These setting lead to offer of additional guidance of special situation due to increase use of liquid based cytology necessitated developing application such as in specimen obtained from post radiation patient to assess cellularity in specimen[29].

Embryology-Under four heading female genital system development occur- **mesoderm, primordial germ cell,coelomic epithelium, and mesenchyme .**During mullerian

organogenesis, uterine development take place along with there is development of upper part of vagina, cervix and both fallopian duct[30].

Anatomy-Lower part of uterus is known as cervix which is an organ of female genital tract. This is the1 connecting part of vagina and main body of uterus, act as gateway between them.

Anatomy and histology of cervix is distinct from uterus and considered as separate structure[31].

The ectocervix and the endocervical canal is the two regions of cervix which composed it. Projection of cervix in vagina is known as ectocervix. Stratified squamous non keratinised epithelium is lining of ectocervix[32]. The transition from the ectocervix and the endocervical canal is the external os which is opening of ectocervix.

More proximal and inner part of cervix is endocervix or endocervical canal, mucus secreting simple columnar epithelium form its lining. The narrow opening is called internal os, where cervix ends and uterus opens[33].

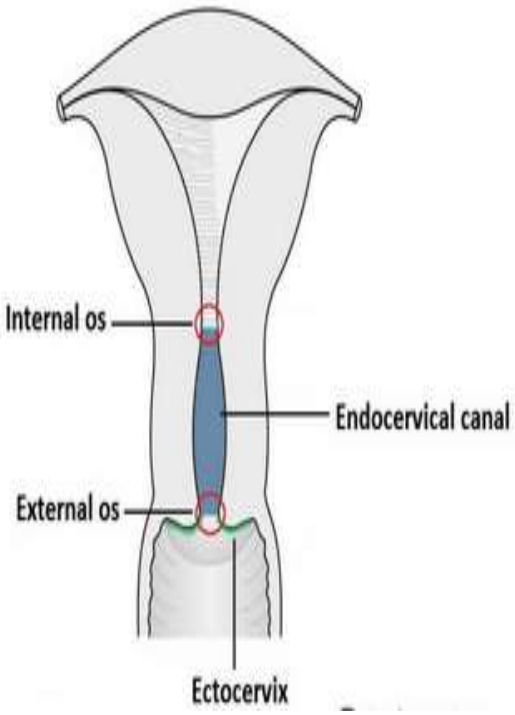


FIG-The ectocervix, endocervical canal and their opening

FUNCTIONS-

There are two main functions performed by cervix-

- Passage of sperms into uterine cavity is facilitated by cervix by dilation of internal and external os.
- Upper female reproductive tract sterility is maintained by cervix. All structures superior to cervix and cervix itself are sterile. The uterine cavity and upper genital tract is protected by bacterial invasion by cervix[34]. The frequent shedding of endometrium, thick cervical mucus and a narrow internal os maintain the inner environment.

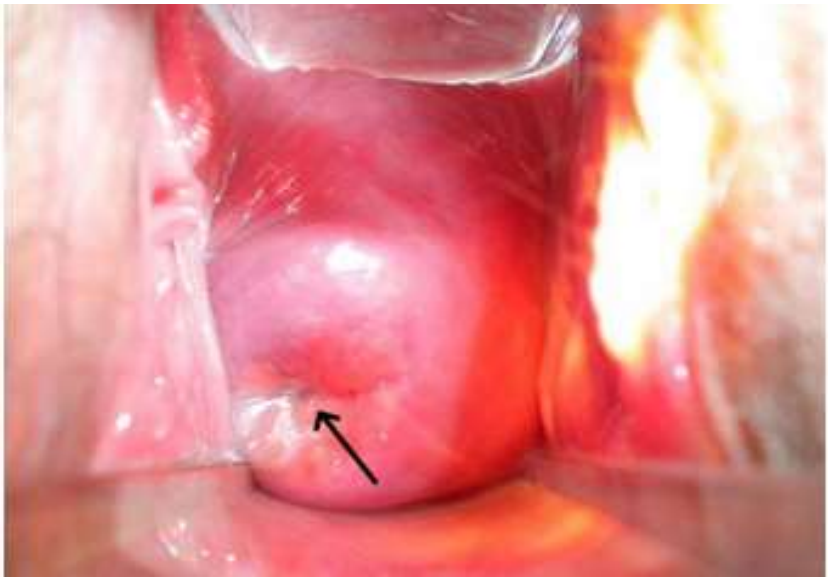


Fig-The ectocervix visible via speculum inserted into vagina, the external os is marked with an arrow.

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE

The uterine artery supplies blood to uterus. The uterine vein is drained by plexus in the broad ligament and this is the venous drainage of uterus.
Iliac sacral inguinal and aortic lymph nodes are the lymphatic drainage of uterus[35].

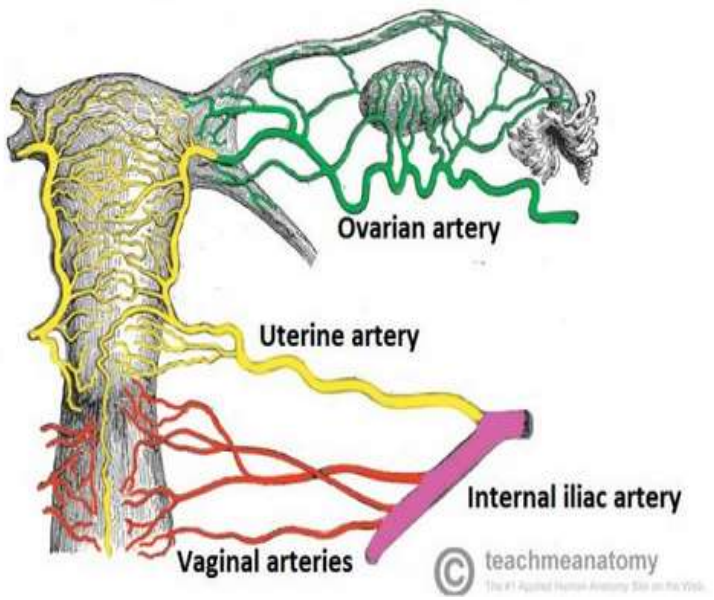


Fig-Posterior view of arterial blood supply to the female reproductive tract

CLINICAL RELEVANCE= DISORDERS OF CERVIX

CERVICITIS- Chronic inflammation and infection of cervix is known as cervicitis Chlamydia trachomatis and Neisseria gonorrhoea are most common cause of cervicitis[36].

Patients present with no symptoms, or may present with pelvic pain, vaginal discharge, postcoital bleeding dyspareunia. Pelvic inflammatory disease may be one of complication of cervicitis in which there is mucus secreting duct blockage and formation of cyst[37]. This will lead to hostile condition for sperm that will lead to infertility.

Cervical cancer

There are following type of cervical cancer-

Squamous cell carcinoma- Ectocervical epithelial lining cancer.

Adenocarcinoma-Cervical gland cancer.

Majority of cervical cancer is caused by Human Papilloma Virus causing infection of female genitelia. Vaccination against HPV is the latest vaccination for cervical cancer[38].

THE 2014 BETHESDA SYSTEM FOR CERVICAL CYTOLOGY

- SPECIMEN TYPE
- SPECIMEN ADEQUECY
- GENERAL CATOGERIGETION
- INTERPRITETION/ RESULT
- ANCILLERY TEST
- AUTOMATED REVIEW
- EDUCATIONAL NOTES AND SUGGESTION(OPTIONAL)

TYPE OF SPECIMAN –conventional (Pap smear) or liquid based preparation-

Conventional Pap-

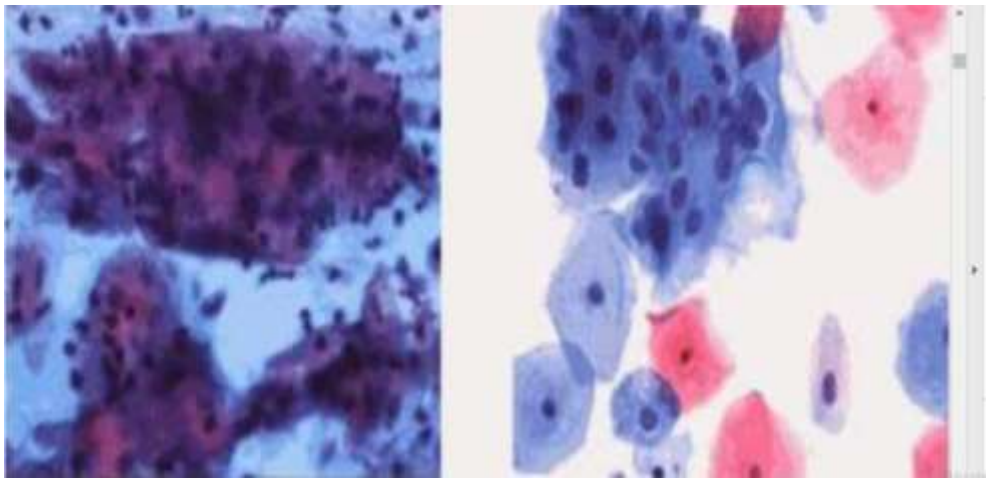
In conventional Pap smears, samples are smeard directly onto a microscopic slide after collection.

Liquid based cytology -

The samples of epithelium collected from transitional zone

Liquid based cytology uses an arrow shaped brush

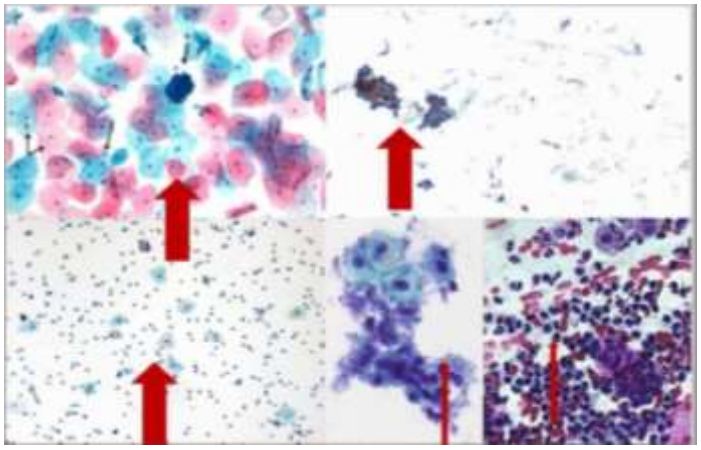
The cells taken are suspended in a bottle of preservative and transported to laboratory



Conventional Pap smear Thin prep Pap test slide

ADEQUECY OF SPECIMEN –

- Satisfactory for evaluation-(endocervical or transformation zone present or absent) other quality indicator like partially obscured by blood or inflammation
- Unsatisfactory for evaluation
  -Rejected or unprocessed smear
  -Processed and examined specimen but unsatisfactory for evaluation
- Minimum squamous cellularity criteria:
  5000 well preserved/ well visualised squamous cell in liquid based preparation
  8000- 12000 cells in conventional smears.
- Endocervical / transformation zone component
  10 well preserved endocervical/ squamous metaplastic cell singally or in cluster.



?

GENERAL CATEGORISATION

- Negative for intraepithelial lesion or malignancy
- Endometrial cell present in a woman of age >45 years
- Squamous or glandular – epithelial cell abnormality

INTERPRETATION / RESULT

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY

(When cellular evidence of neoplasia is absent)

NON NEOPLASTIC FINDING

Cellular non neoplastic finding:-

-metaplasia of squamous type

-changes associated with keratosis

-metaplasia of tubal type

-changes associated with atrophy

-changes associated with pregnancy

- changes associated with reactive cellularity

-cervicitis induced by lymphocyte

-inflammation in typical repair

-barrier method of contraceptive devise

- post hysterectomy glandular tissue

ORGANISM

-T. vaginalis

-Candida and morphologically similar organism

-bacterial vaginosis associated with shift of flora

-Actinomyces like bacteria

-Herpes simplex associated cellular changes

-CMV associated cellular changes

OTHER

-In women of >45 years presence of endometrial cells

(Mention if negative for intraepithelial lesion)

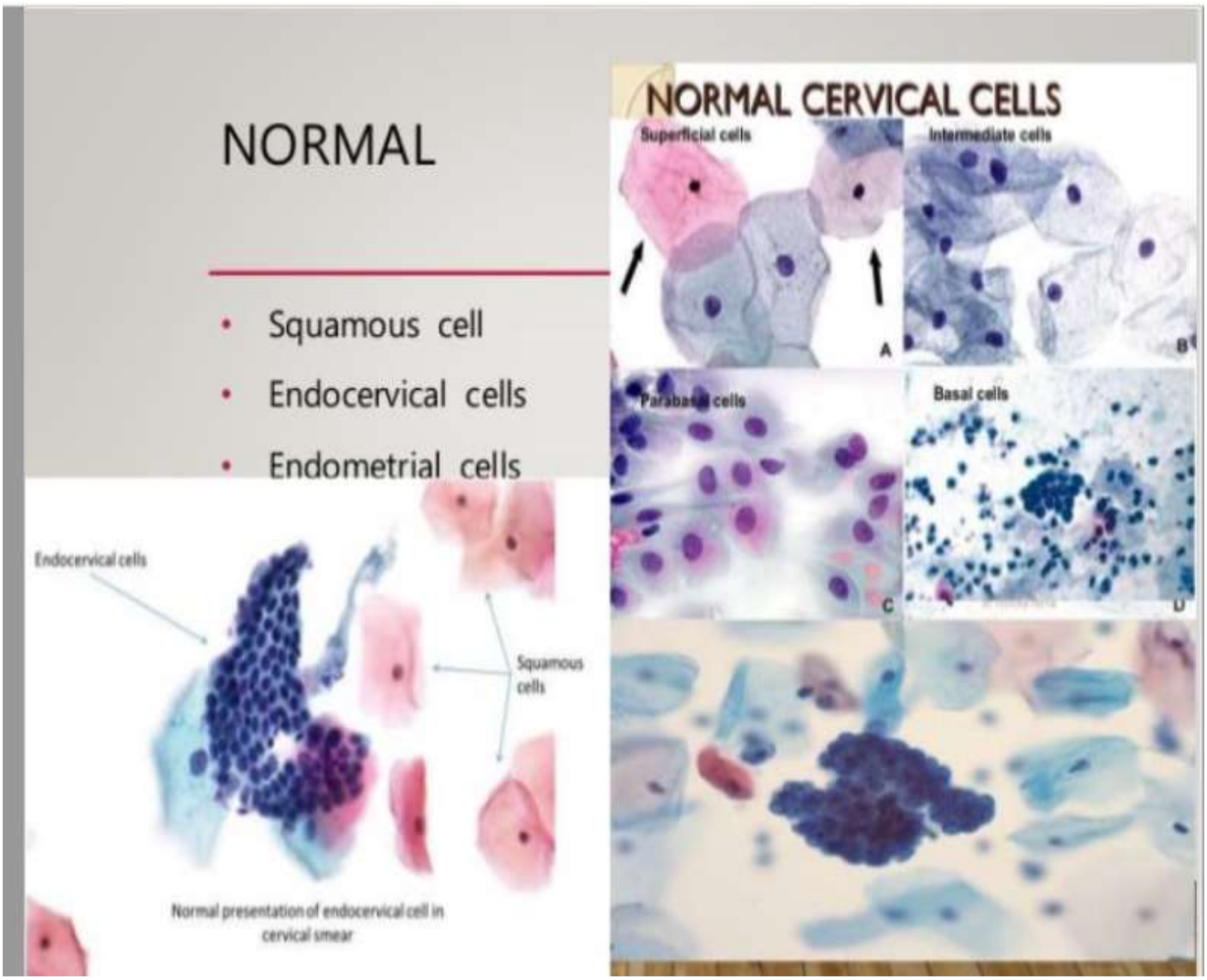
EPITHELIAL CELL ABNORMALITY

SQUOMOUS CELL

- Atypical squamous cell
  -of undetermined significance (ASCUS)
  -cannot exclude HSIL(ASC-H)
- Low grade intraepithelial lesion(LSIL)
  (HPV /mild dysplasia /CIN1)
- High grade intraepithelial lesion(HSIL)[39]
  (CIS/CIN2/CIN3 moderate to severe dysplasia)
  -If invasion is suspected then features of invasion
- SCC

It is a system of reporting cervical or vaginal cytologic diagnosis used for reporting Pap smear result.

It was introduced in 1988, revised in1991, 2001 2014[40].



Superficial squamous cell: mature and polygonal
Cytoplasm- mostly eosinophilic
Nucleus- pyknotic

cells shows relatively prominent cellular outline.

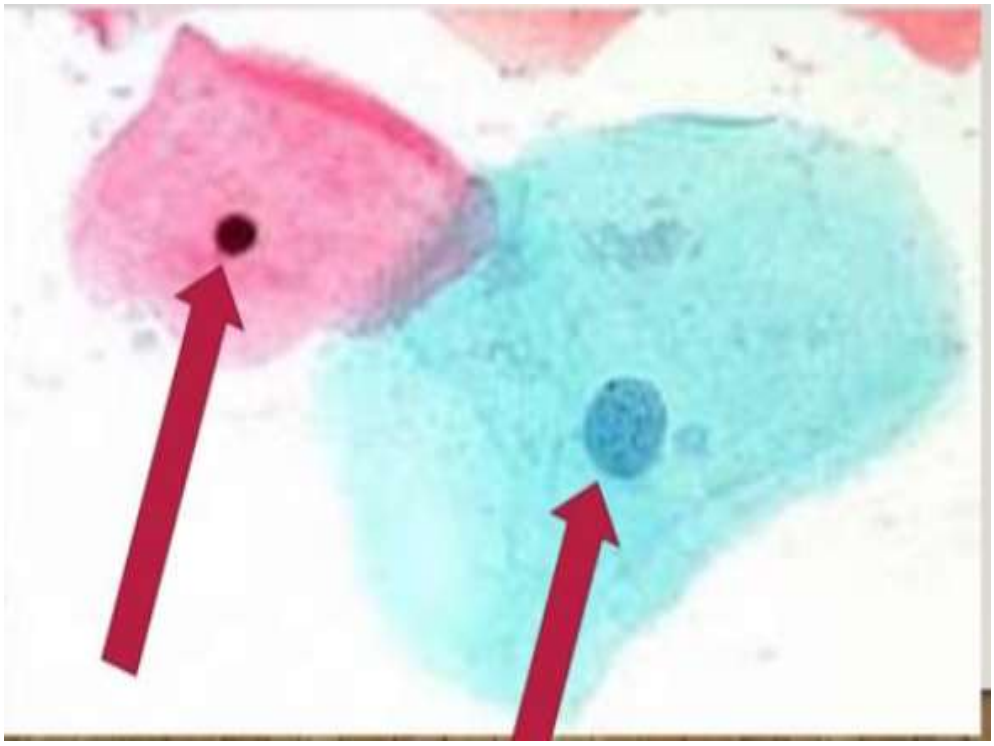


Fig-Mature squamous cell and intermediate cell

- Intermediate squamous cell : Mature

  cytoplasm - Cyanophilic

  nucleus - non pyknotic ,vesicular nucleus

  large oval / rounded nuclei with groove

  granular chromatin

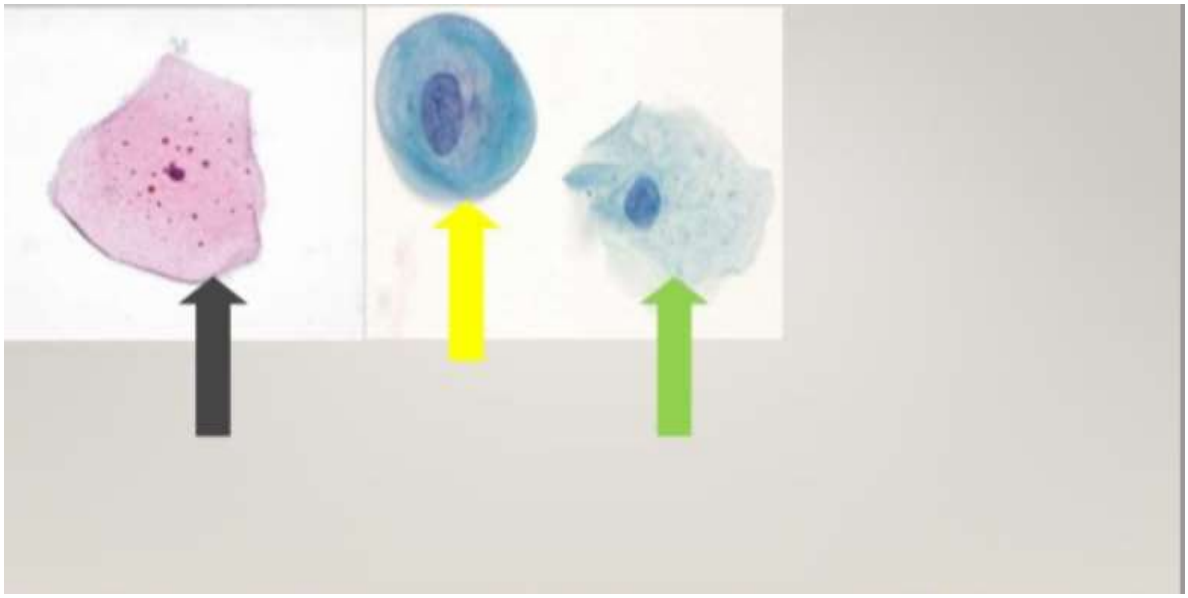
- Parabasal / Basal squamous cells :

  small , oval , round

  immature

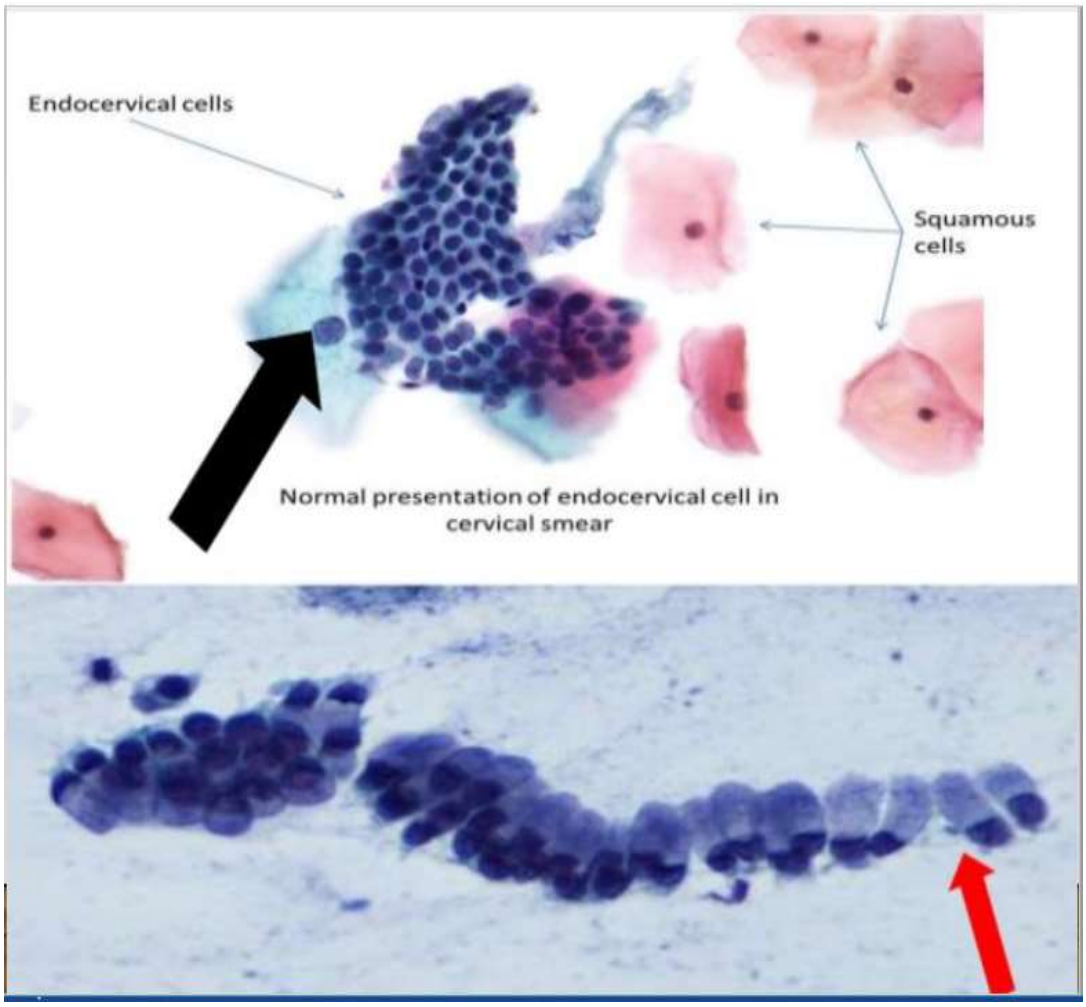
  cytoplasm - cyanophilic / eosinophilic

  nucleus – oval, fine chromatin



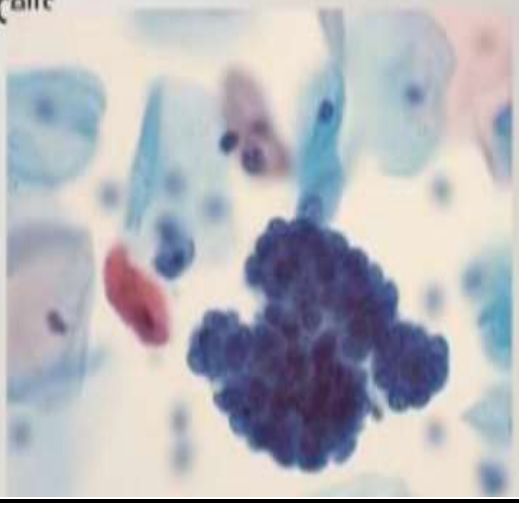
ENDOCERVICAL CELLS

- Columnar in shape and contain mucin
- In cervical smear, endocervical cells arranged singly in layers and in sheets forming a palisade
- Honey comb or picket fence appearance
- Nucleus is large, round and placed at basal portion
- nucleus is large rounded and placed at basal portion
- nucleus is granular with evenly distributed chromatin
- Cytoplasm- eosinophilic/ basophilic.



Endometrial cells :

- ✓ in smears appear as rounded clusters
- ✓ central core of connective tissue with elongated cells (stromal)surrounded by round- oval cells(glandular) - Exodus
- ✓ cytoplasm - scanty , vacuolated
- ✓ nucleus - size similar to intermediate cells
  - karyorrhexis
- ✓ cell border - ill defined
- ✓ histiocytes



Endometrial cells:

- In smears appear as rounded clusters
- Central core of connective tissue with elongated cells(stromal) surrounded by round – oval cells – Exodus
- Cytoplasm – scanty vacuolated
- Nucleus – Karyorrhexis
- Cell border – ill defined
- Histiocytes

In liquid based preparation, exfoliated endometrial cells may be slightly larger, with more easily visible nucleoli and enhanced chromatin detail compared to conventional smear preparations.

NILM – NON NEOPLASTIC FINDING

- Non neoplastic cellular variation
- Squamous metaplasia:
    - ✓ Nucleus – round to oval
    - ✓ Evenly distributed chromatin

NILM – NON NEOPLASTIC FINDING

-Non neoplastic cellular variation
-keratotic cellular change

- ✓ Keratosis
- ✓ Hyperkeratosis
- ✓ Parakeratosis
- ✓ Dyskeratosis

Parakeratosis

-Squamous cells with dense orangophilic or eosinophilic cytoplasm
-Cells – isolated in sheets and in whorls
-Cell shape – round / polygonal / spindle shaped

Hyperkeratosis

-Anucleate squamous cells with ghost like nuclear
Features

NILM – NON NEOPLASTIC FINDING

-Non neoplastic cellular changes
-TUBAL METAPLASIA
-Nucleus- round – oval, pleomorphic
Hyperchromatic
-N:C ratio – high
Cytoplasm- vacuoles / goblet cell change

NILM – NON NEOPLASTIC FINDING

-non neoplastic cellular changes
-ATROPHY
-flat monolayer sheets of parabasal like cells
-nuclear enlargement, N:C ratio, regular contour
-abundant exudate (inflammatory)

NILM – NON NEOPLASTIC FINDING

Pregnancy related cellular changes

-Navicular change – boat shaped intermediate cells
Abundant basophilic clear cytoplasm
Nucleus- vesicular, delicate chromatin
- Decidua
-Cytotrophoblast and syncytotrophoblast
-Arias Stella reaction

NILM – NON NEOPLASTIC FINDING

Reactive cellular changes
<u>-Inflammation-</u>
-Reactive squamous cells – mild nuclear enlargement
Without significant chromatin abnormality
-Reactive endocervical cells- variation in nuclear

size,

Prominent nucleoli, fine chromatin,
-perinuclear halo

NILM- NON NEOPLASTIC FINDING

Reactive cellular change
-Lymphocytic (follicular) cervitis

NILM- NON NEOPLASTIC FINDING

Reactive cellular change
-radiation
Cell size, bizarre shape
Nuclear size /Normal/ Binucleation / Multinucleation
Cytoplasm – vacuolated, polychromatic, intracytoplasmicPML

NILM- NON NEOPLASTIC FINDING

Reactive cellular change
-IUCD
Glandular cell – singly / clusters in clean background

NILM- NON NEOPLASTIC FINDING

-glandular cell change post hysterectomy
Benign appearing glandular cells

NILM – ORGANISM

Trichomonasvaginalis
Pear shaped cyanophilic
Nucleus – pear, vesicular, eccentrically
Cytoplasm – eosinophilic granules
Flagella
Leptothrix

NILM – ORGANISM

Candida

Budding yeast & pseudo hyphae
In liquid based preparation: spreading of epithelial cells/ shish kebab effect

NILM – ORGANISM

Bacterial vaginosis
Clue cells

NILM – ORGANISM

Actinomyces
Cotton ball clusters

NILM – ORGANISM

HSV
Nucleus – ground glass appearance
Dense eosinophilicintranuclear inclusions
Large multi nucleated / mononucleated squamouscells

NILM – ORGANISM

CMV
Endocervical glandular cells affected
Large eosinophilicintranuclearviral
Inclusion with halo

INTERPRETATION / RESULT

OTHERS:
Endometrial cells (in a woman of age >=40Years of age)
(Specify if negative for squamous Intraepithelial lesion)

INTERPRETATION / RESULT

EPITHELIAL CELL ABNORMALITIES
SQUAMOUS CELLS

Atypical squamous cells - of undetermined significance (ASC-US)
-Cannot exclude HSIL (ASC-H)

Low grade squamous intraepithelial lesion (LSIL)
(Encompassing HPV / mild dysplasia/CIN1)

High grade squamous intraepithelial lesion (HSIL)
(encompassing moderate and severe dysplasia CIN2 and CIN3)
with features suspicious for invasion (if invasive)

INTERPRETATION / RESULT

EPITHELIAL CELL ABNORMALITIES
GLANDULAR CELL

Atypical
Endocervical cells (not otherwise specified or specify in Comments)
Endometrial cells NOS or specify in comments)
Glandular cells NOS or specify in comments

Atypical
Endocervical cells, favour neoplastic glandular cells, favour neoplastic

Adenocarcinoma in situ
Endocervical
Endometrial
Extrauterine
Not otherwise specified

INTERPRETATION / RESULT

OTHER MALIGNANT NEOPLASM (SPECIFY)

Uncommon primary tumors of cervix & uterine corpus
Carcinomas (spindle scc, poorly diff scc)
Neuroendocrine (small cell, large cell
carcinoid glassy, mucinous, clear cell sarcoma)
Secondary/metastatic tumour
Extra uterine carcinomas (Breast Stomach Ovary Colon Kidney Bladder)

INTERPRETATION / RESULT

ASC

ASC-US

Changes that are suggestive of LSIL but are insufficient for definitive interpretation

ASC
- Squamous differentiation
- N:C ratio
- Nuclear size enlarged hyperchromasia
  Clumped chromatin, irregular multinucleated
  Seen in atypical parakeratosis, atypical repair,
  Atypia in postmenopausal woman.

INTERPRETATION / RESULT

LSIL

Cells – singles / clusters / sheets

Nucleus – enlarged, hyperchromatic, anisonucleosis
Chromatin is coarsely granular to smudgy
Binucleate / multinucleated

INTERPRETATION / RESULT

HSIL

Cells
- Smaller than LSIL
- Singly / sheets / syncytial aggregates
  Hyperchromatic crowded group

Nucleus – enlarged, high N:C ratio than LSIL
Irregular nuclear membrane

INTERPRETATION / RESULT

SCC- Keratinising SCC
- Non keratinising SCC

Keratinising SCC

Cells- variable sizes & shapes,
Keratinised tadpole cells

Nucleus-vesicular or pyknotic

Cytoplasm- deeply eosinophilic / cyanophilic

Background – tumor diathesis

INTERPRETATION / RESULT

SCC – Keratining SCC

Non keratinising SCC

Non keratinising SCC
Cells – singly / syncytial aggregates

Nucleus-irregular coarsely clumped chromatin
Nucleoli prominent
Features of HSIL
Background –tumor diathesis

INTERPRETATION / RESULT

Atypical endocervical cells NOS
Cells – sheets, cell crowding
Nucleus - overlapping, enlarged nucleoli
- High N:C ratio

INTERPRETATION / RESULT

Atypical endocervical cells, favour neoplastic
Cells – sheets, strips, rosettes / feathering
Ill-defined borders
Nucleus – crowding, overlap, enlarged

INTERPRETATION / RESULT

Atypical endometrial cells
Cells – small group (5-10 cells)
Ill-defined border
Nucleus – enlarged
- Mild hyperchromasia
- Chromatin heterogeneity
Cytoplasm- vacuolated & scanty

INTERPRETATION / RESULT

Adenocarcinoma in situ
Cells – sheets, clusters, rosettes nuclear crowding overlap, feathering
Nucleus- enlarged, hyperchromatic, increased N:C
Coarsely granular chromatin, mitoses
Apoptotic bodies
Cytoplasm- less
Background- clean

INTERPRETATION / RESULT

Adenocarcinoma

Endocervical Adenocarcinoma
Endometrial Adenocarcinoma

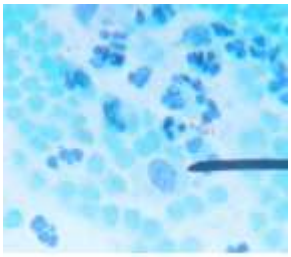


FIG- showing Squamous Metaplasia

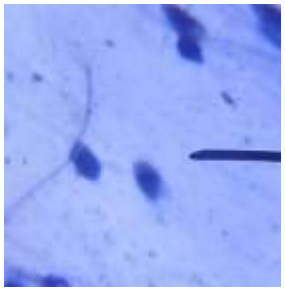


FIG –showing reactive cellular changes

FIG- showing Atypical endometrial cell NOS

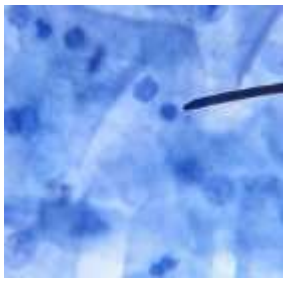


FIG-showing ASCUS

FIG- LSIL

Screening Guide Lines

Recommendations for cervical cancer screening are slightly conflicting.

The American Cancer Society (ACS) updated recommendations of 2002 states that

- By using Pap method screening is done every year. On using LBC two yearly screening should be done.

- Screening has to be done either at 21years of age or in 3 years of the beginning of sexual action. At 70 years of age, if the Pap reports were normal for the precedent 10 years screening has to be stopped.

- Screening after hysterectomy for benign disease is not necessary.

The American College of Obstetricians and Gynaecologists (ACOG) differs from the ACS recommendations by stating that

- Women younger than the age of 30 should undergo cervical cytology screening yearly and in those older than the age 30 if there is no associated risk factors screening should be done once in 2 to 3 years using either LBC or conventional Pap testing furthermore. According to ACOG, women who are 30 and above ideally should undergo both cytology and HPV DNA testing. If results are negative using this combination, a woman can be retested at only 3 year intervals (19) (Table-1). The negative predictive value of this combination test exceeds 99%. In women younger than 30 years, the high prevalence of high risk HPV infection makes this strategy too nonspecific for use.

Table – 1: Comparison of Cervical Cytology Screening[41]

Guide line	**American Cancer Society (ACS)**	**ACOG**
Initial screening	Age 21 or 3 years after sexual activity	Same as ACS
Interval	• Every year for conventional Pap • Every 2 years for LBC • Every 2-3 years after age 30 with 3 consecutive normals	• Every year for either LBC or conventional smear • Every 2-3 years after age 30 with 3consecutive normal
Discontinue	• Age 70 if 3 consecutive normals in 10 years	• No upper age limit

METHEDOGY AND STATISTICS

Study Design

The study design was observational cross sectional study.

Place of study and sample frame

This study was conducted at **SANTOSH MEDICAL COLLEGE AND HOSPITAL, Ghaziabad, and Uttar Pradesh** and samples were be received from department of obstetrics and gynaecology.

Period of study

The study was conducted on the cases from O.P.D. and admitted patients requiring Pap smear in cervical lesions. Patients of reproductive age group were enrolled in the study.

Sample size

A total of 130 cases were enrolled in this observational study.

LABORATORY TESTING

By putting the patient in dorsal position, per speculum examination was done, after visualisation of the cervix. Conventional Pap smear was collected by using the Ayer's spatula and the cells were smeared on the glass slide. The glass slide was fixed immediately with 1:1 mixture of 95% ethyl alcohol and ether, and then the slide was sent to the laboratory for processing, where the smear was stained with papanicolaou stain and was reported

Fig: Showing conventional PAP smear

Cytology reporting

Reporting of cytology examination in our study was done using the Bethesda System's 2001 modification. The abnormality in cytology specimen is due to infection, inflammation, reparative changes, and epithelial cell abnormality. The epithelial cell abnormality includes low –grade (LSIL) squamous intra epithelial lesion, high- grade

(HSIL) squamous intraepithelial lesion, and atypical squamous intraepithelial lesion. All cytology specimens were classified either as satisfactory or unsatisfactory. Unsatisfactory specimen was due to scanty cells, improper fixation of slide, debris, mucus, blood cells, inflammation, and other factors which obscure 75% or more of epithelial cells. The specimen was considered to be satisfactory if they contain 5000-10000 well preserved and well visualised squamous cells along with cells from transformation zone. For the purpose of tabulation, cases whose smears showed infective organisms and all unsatisfactory smears in both cytology methods were considered as cases with normal reports

Sample Size Determination

The sample size for the study was determined using the proportion method.

For small population formula:

$$n = \frac{z^2 \times (p \times q)}{e^2} \times \sqrt{\frac{N - n}{N - 1}}$$

Where,

n = Sample Size

Z= Standard Scored associated with 95% level of confidence (1.96)

p x q = Variability [since p & q were unknown, the worst case scenario was considered. Thus, p = was taken as 0.5 and q= 0.5

e= (error) = 5%

N= Population Size [411] [21].

n= Sample Size [384]

$$n = \frac{z^2 \times (p \times q)}{e^2}$$

$$= \frac{(1.96)^2 (0.5)(0.5)}{(0.05)^2}$$

$$= \frac{3.84 \times 0.25}{0.0025}$$

$$= \frac{0.96}{0.0025}$$

$$= 384$$

Thus, the sample size calculated as follows:

$$= 384 \times \sqrt{\frac{N - n}{N - 1}}$$

$$= 384 \sqrt{\frac{411 - 384}{410}}$$

$$= 384 \sqrt{\frac{27}{410}} \qquad = 384 \text{ x } 0.26$$

N = 130 (Sample Size)

Inclusion criteria

Persons giving consent for Pap smear.

Exclusion criteria

Persons not giving consent for Pap smear.

Method of collection of data

A predesigned semi-structured questionnaire was prepared based on the review of literature on Pap smear. A pilot study on 10 cases was done to understand the feasibility, reliability and validity of the questionnaire. After the pilot, the corrections were made in the questionnaire based on the further review of literature and advice/suggestions of the guide of the study. Then the final questionnaire was presented in front of the guide and after corrections it was used for the data collection among the study participants.

After taking the patient's written, informed, valid consent, recruitment was done prior to the commencement of the study. During the period of prospective data collection, demographic details of the recipients and the details of clinical presentation and pap smear was evaluated to ascertain whether the indications for pap smear is appropriate according to the standard guidelines and if re-estimation of parameters was carried out within the specified time.

After taking aseptic precautions, with the help of Ayre's spatula cervical scrapings was collected by the qualified gynaecologist from transitional zone, wet fixed in 95% alcohol and sent to the pathology department where all the details in requisition forms were checked along with the supplied slides and pap staining was performed. Later on slides was examined microscopically under low power and high power.

The data collection will include Name, Age, Sex, Department, Hospital numbers, Inpatient numbers, History and Examination, Routine investigations, Special investigations, Radiological investigations, Pap smear, Histopathological examination (Whenever possible) and final diagnosis. At the end of every day, all the forms were checked for their completeness of the data. Those forms which have incomplete information or information which is not comprehensible were completed on the next day.

Data analysis

Statistical software to be used: SPSS 24 version was used for the analysis of the data.

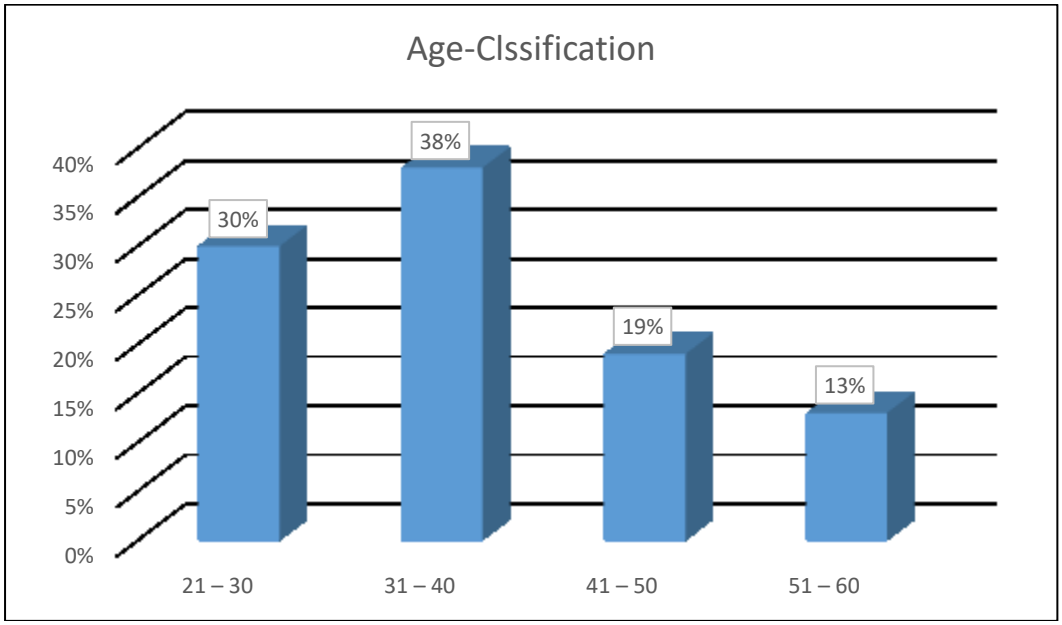
Statistical test to be applied:Descriptive statistics like mean, percentage and standard deviation was used. The results were expressed in the form of bar diagrams, pie charts and pictographs and compared with other similar studies done in the past as well as with newer studies, if any. The significance of results were found out and discussed.

RESULTS

The present study was carried out on 130 patients who were randomly selected from the Department of Pathology at SMC Ghaziabad UP. After taking history and clinical examination cytology specimens were collected for Pap test for all patients.

Table -2.: Age wise distribution of cases[42]

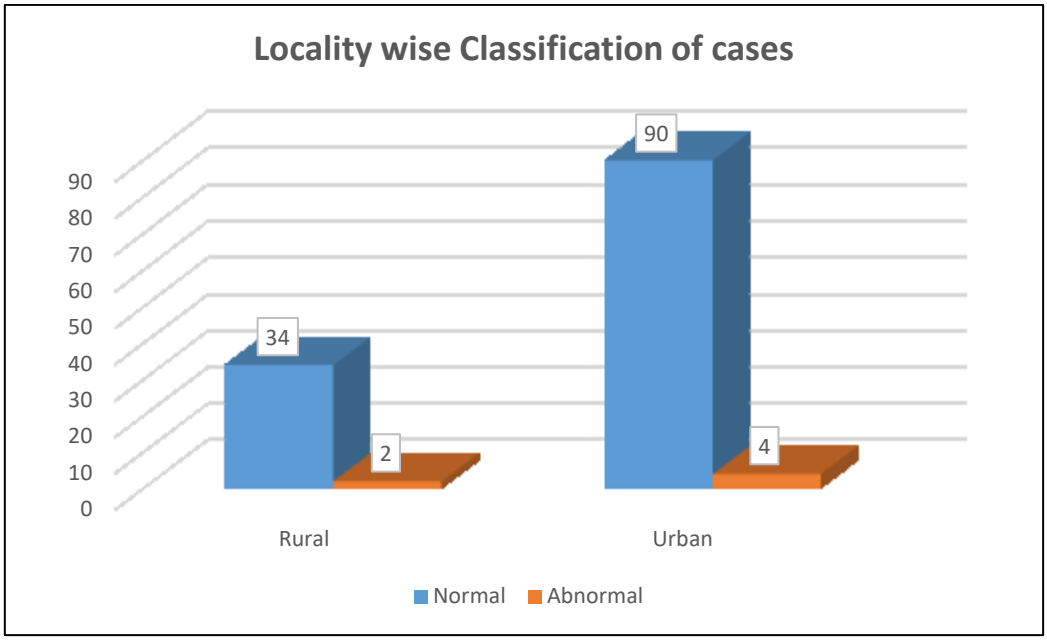
Age (years)	Cases	Percentage
21 – 30	40	30 %
31 – 40	50	38 %
41 – 50	25	19 %
51 – 60	15	13 %



It is noted in our study that out of total 130 cases, 40 cases (30%) studied belonged to third decade of life, 50 cases (38%) belonged to fourth decade of life, 25 cases (19%) belonged to fifth decade of life, and 15 cases (13%) belonged to sixth decade of life.

Table-3: Locality wise case distribution[43]

Place	Total cases	Normal	Abnormal
Rural	36	34	2
Urban	94	90	4



In the present study out of 130 cases, 36 cases were from rural area and 94 cases were from urban area. Of the abnormal cases 2 cases (33.3%) were found to be rural area and 4cases (66.6%) were found to be urban area.

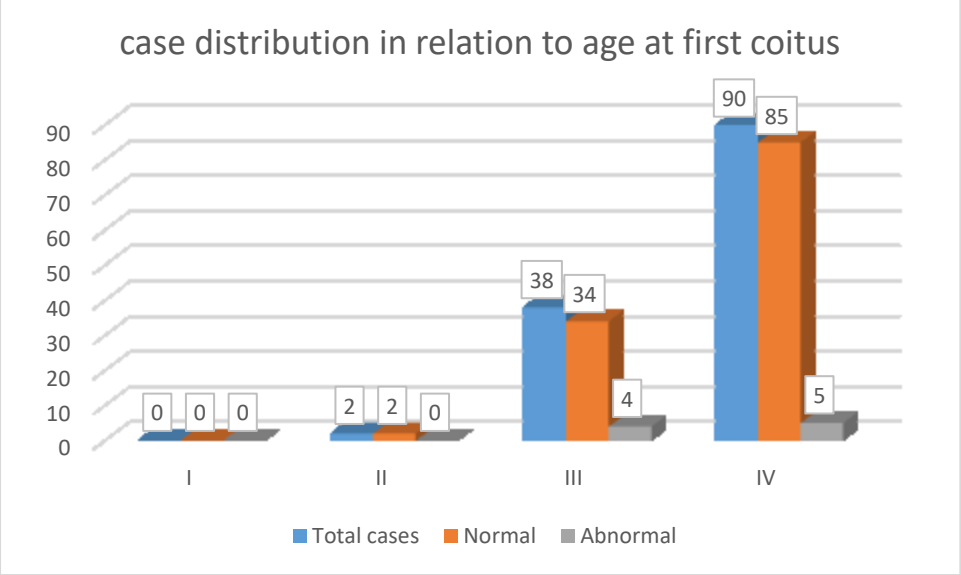
Table-4: Socio economic class wise case distribution[44]

SE class	Total cases	Normal	Abnormal
I	-	-	-
II	2	2	-
III	38	34	4
IV	90	85	5

It is noted in our study that out of 130 cases, 90 cases belonged to socio economic class IV (Modified Kuppuswamy's Scale), 38 cases belonged to socio economic class III, 2 case from socio economic class II. Of the abnormal cases 4 cases (44.4%) belonged to socio economic class III and 5 cases 55.5%) cases belonged to socio economic class IV

Table-5: Case distribution in relation to age at first coitus[45]

Age at first coitus(years)	Total cases	Normal	Abnormal
Less than 20	63	43	20
21-25	65	60	5
26-30	2	2	-

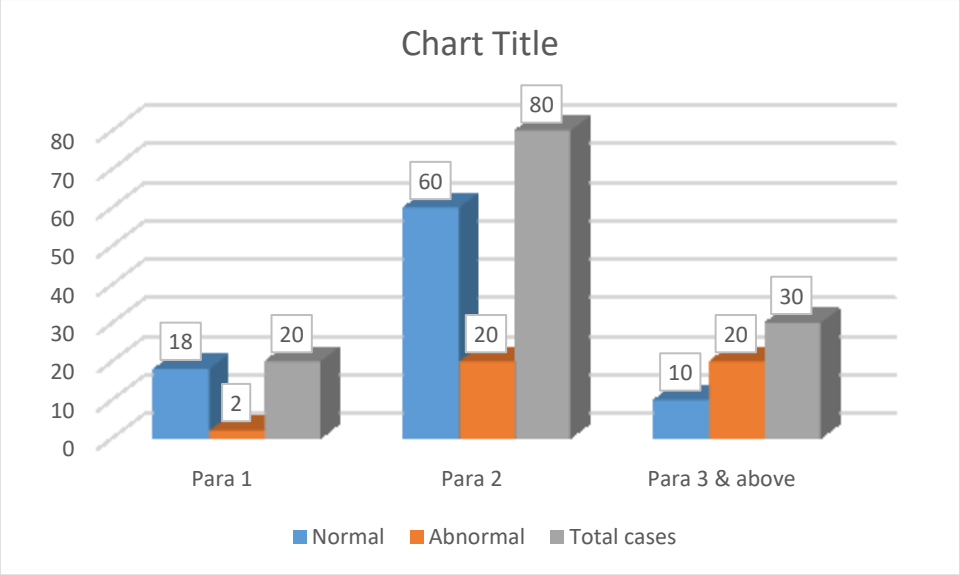


In our study 63 cases started sexual activity less than 20 years of age, 65 cases had first coitus between 21-25 years of age and 2 cases between 26-30 years of age.

Of the total 25 abnormal cases 20 (80%) cases started sexual activity less than 20 years of age, 5 cases (20%) started sexual activity between 21-25 years of age and no CIN cases were detected in women who had first coitus between 26-30 years of age.

Table-6: Case distribution in relation to Parity index[46]

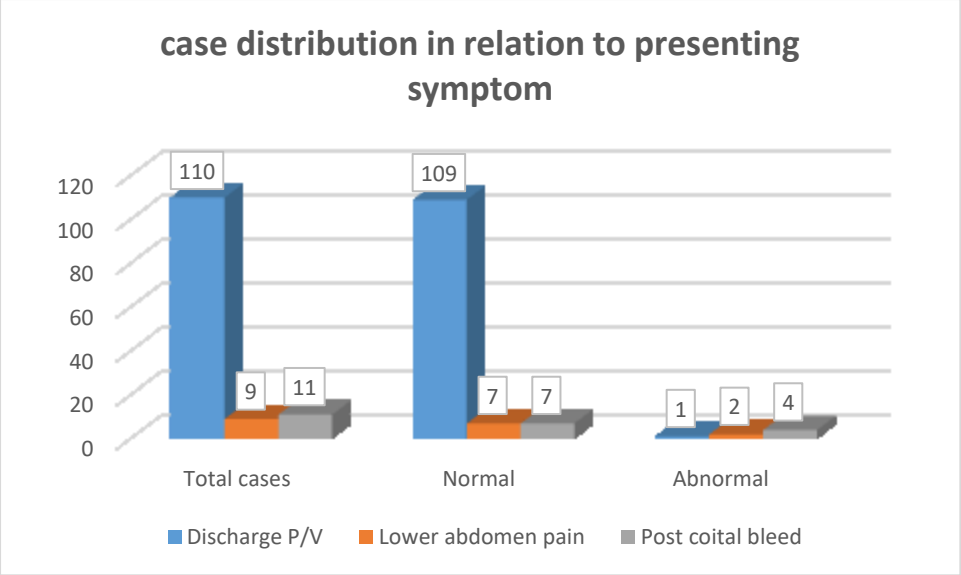
Obstetric score	Total cases	Normal	Abnormal
Para 1	20	18	2
Para 2	80	60	20
Para 3 & above	30	10	20



In the present study out of 130 cases, 20 cases belonged to Para 1, 80 cases belonged to Para 2 and 30 cases belonged to Para 3 and above. 20 (47%) out of 30 abnormal cases had Para 3 and above, 20 cases (47%) belonged to Para 2, and 2 case (4%) belonged to Para 1.

Table-7: Case distribution in relation to presenting symptoms

Symptoms	Total cases	Normal	Abnormal
Discharge P/V	110	109	1
Lower abdomen pain	9	7	2
Post coital bleed	11	7	4

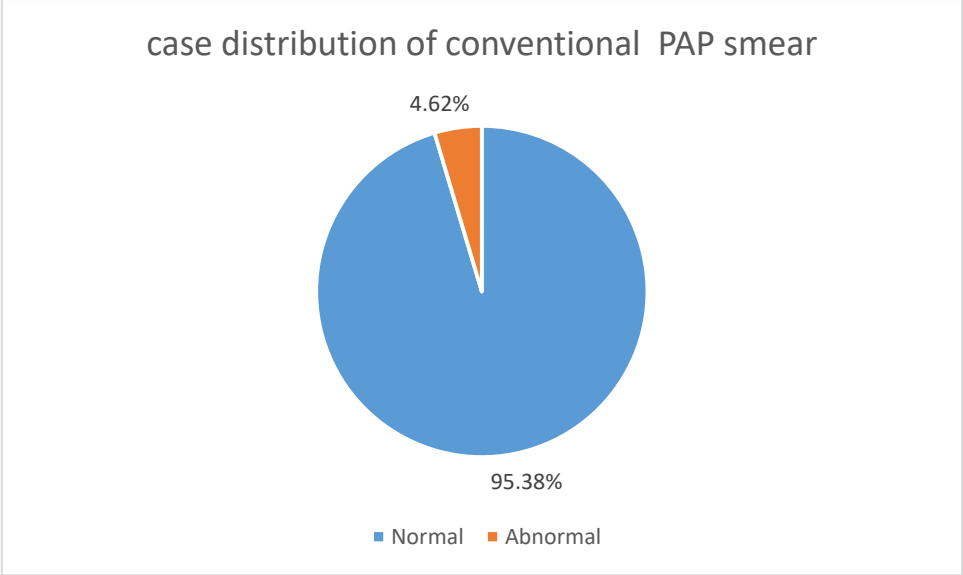


In our study out of 130 cases, 110cases presented with symptoms of vaginal discharge, 9cases with lower abdomen pain, 11 cases with post coital bleed.

1 (14%) out of 7 abnormal cases presented with discharge P/V, 2 cases (28%) with lower abdomen pain and 4 cases (57%) presented with post coital bleeding.

Table-8: Case distribution of Conventional Pap smear

Cytology	Normal	Abnormal
PAP	124	6



In Conventional Pap smear 124 (95%) cases were normal and 6 cases (5%) showed abnormality.

Table 9:Case Distribution Of Satisfactory and Unsatisfactory Pap smear

Cytology	Satisfactory smear	Unsatisfactory smear
PAP	119	11

In the present study out of 130 cases, in PAP 119 smears were satisfactory for evaluation and 11 smears were unsatisfactory for evaluation. Unsatisfactory smear in Pap smear it is due to thick smear caused by obscuring mucus.

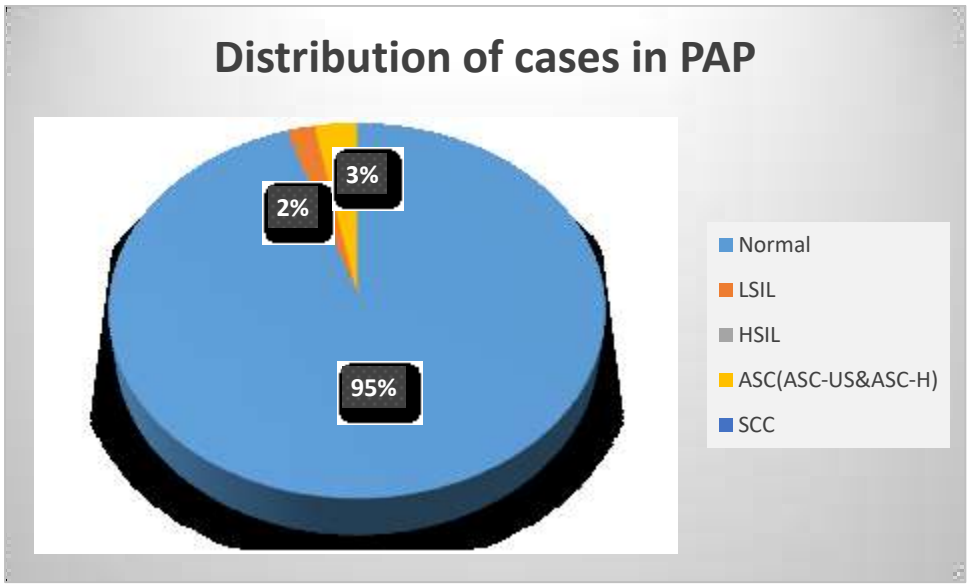
Table-10: Comparison of Infectious agent in PAP

Infectious agent	PAP
Total cases	3
Bacterial Vaginosis	1
Candida	-
Trichomonasvaginalis	2

Pap smear showed infectious agents in 3 cases (3%) of these 2 cases showed features of Trichomonasvaginalis and 1 case showed features of Bacterial vaginosis.

Table – 11:Distribution of cases in PAP

Bethesda category	PAP	Percentage
Normal	124	95
LSIL	2	2
HSIL	-	-
ASC (ASC-US & ASC-H)	4	3
SCC	-	-



Out of 130 cases, in Conventional Pap smear 2 cases (2%) showed LSIL, ASC was seen in 4 cases

DISCUSSION

Screening for cervical cancer has resulted in the reduction of of cancer cervix and its complications. Pap smear has been used for the screening purpose since 1940's but studies have shown that the sensitivity of a single Pap test is low and it has high false negative rate. This is said to be due to improper sampling and ineffective interpretation. In Pap smear only 20% of the scraped cells in the Ayer's spatula are transferred to the slide while smearing, which is done manually. Therefore alternative screening methods which overcome these pitfalls in Pap smear is developed. Earlier age of occurrence of preinvasive cervical lesions and SCC were due to earlier age of marriage in our society.

In India women of low socio economic class and rural women showed higher incidence of cancer cervix **(Vallikad, Kurkure AP, Yeole BB)**. The main explanation specified for this is lack of access to screening and health services and poor knowledge about the risk factors of cancer cervix.

In our study (table-4) 66% of abnormal cases were from urban area in contrast to **Vallikad, Kurkure AP, Yeole BB**). Our observation may be due to random case selection and most of our patients were from urban area.

In our study (table-6) 55.5 % of abnormal cases belonged to class IV socio economic class and 44.4 % belonged to class III socioeconomic class (Modified Kuppuswamy scale), a finding similar to the study by **(Sherwani RK etal, Christopherson and Parker)** in their studies prevalence of cancer cervix cases were more in low socio economic class women with younger age of marriage.

In our study (table-7) 80% of cases with preinvasive lesion had onset of sexual activity at late seconddecade of life, finding which correlates with the study of **Sherwani RK et al and Rotkin**. Rotkinpostulated that cancer cervix is transmitted through sexual intercourse from male to female, with a higher chance. Data's from case – control studies indicate that high parity increases the risk of developing cervical cancer, specifically women with seven prior full term have an approximately four fold risk, and those with one or two have a twofold risk compared to nulliparous.

In our study 47 %(table-7) pre invasive cases had parity index of three or more concordant with **Sherwani RK et al**.

The most common presenting complaint of abnormal cases in our study was discharge per vaginum 14 %, (table- 8)similar to **Sherwani RK et al** and most the patients with post coital bleeding had pre invasive lesion in our study.

In our study unsatisfactory smear for evaluation 8 % in Pap smear similar to the study by **Sherwani RK et al** and **Limaye et al** In the study conducted by Sherwani RK et alun satisfactory smear on Pap smear was 5%; in Limaye et al study unsatisfactory specimen was 0.27% on Pap smear. Most of the unsatisfactory smear in Pap smear is due to thick smear In the present study. Infectious agents were detected in 3% of cases on Conventional Pap smear similar to the study by **Sherwani RK et al**, where infectious agents are found in 3.1% of cases on Pap smear.

Detection of LSIL increased from 2% with conventional Pap smear which correlates with the Finding of **Sherwani RK etal**, **Limaye et al, Diaz – Rosario and Kabawat Sherwani RK et al** reported an increased percentage of cases of LSIL from 10.6%. **Limayeet al** reported that detection of LSIL increased from 0.3%.

In a study conducted by **Zhu et al (2)** there was significantly reduced ASC, 8% with Pap smear**.** It is noted in our study that Pap smear showed 3% of ASC similar to **Zhu et.**

CONCLUSION

1. In the present study Conventional Pap test is good for detection of preinvasive cervical lesions; this is mainly due to elimination of sampling error and decreasing the probability of false negative reports. The main aim of cervical screening test is detection of precancerous cervical lesions. It is obvious in this study Pap test certainly contributes to the achievement of this aim.
2. In our study Sensitivity for the detection of LSIL with Conventional Pap smear was 02%. The increased sensitivity of PAP is increases detection of cytologic abnormality.
3. It is inferred from our findings that Pap test is a good screening methods.

SUMMARY

1The study was conducted on the cases from O.P.D. and admitted patients requiring Pap smear in cervical lesions. Patients of reproductive age group were enrolled in the study Total 130 patients attending the outpatient Department of Pathology at SMC were randomly studied

2. It is noted that out of 130 cases 38% of cases belonged to fourth decade of life.

3. It is noted that 66.6% of abnormal cases were from urban area and 33.3% from rural area

4. In the present study 55.5% of abnormal cases belonged to socio economic class IV

5. In current study, 80% of abnormal cases started sexual activity at less than 20 years of age and no abnormality was detected in women who have started sexual activity after 26 Years of age

6. In the present study 47% of abnormal cases had parity index of 3 and above.

7. It is noted that 14% of abnormal cases presented with symptom of discharge P/V and 57% with post coital bleeding

8. In our study unsatisfactory smear for evaluation was 8% in Pap smear

9. In the present study infectious agent was (3%) in Pap smear.

10. It is noted that Pap smear (LSIL 2%) and it was statistically significant.

11. In our study, ASC prediction was with PAP (3%) it was significant.

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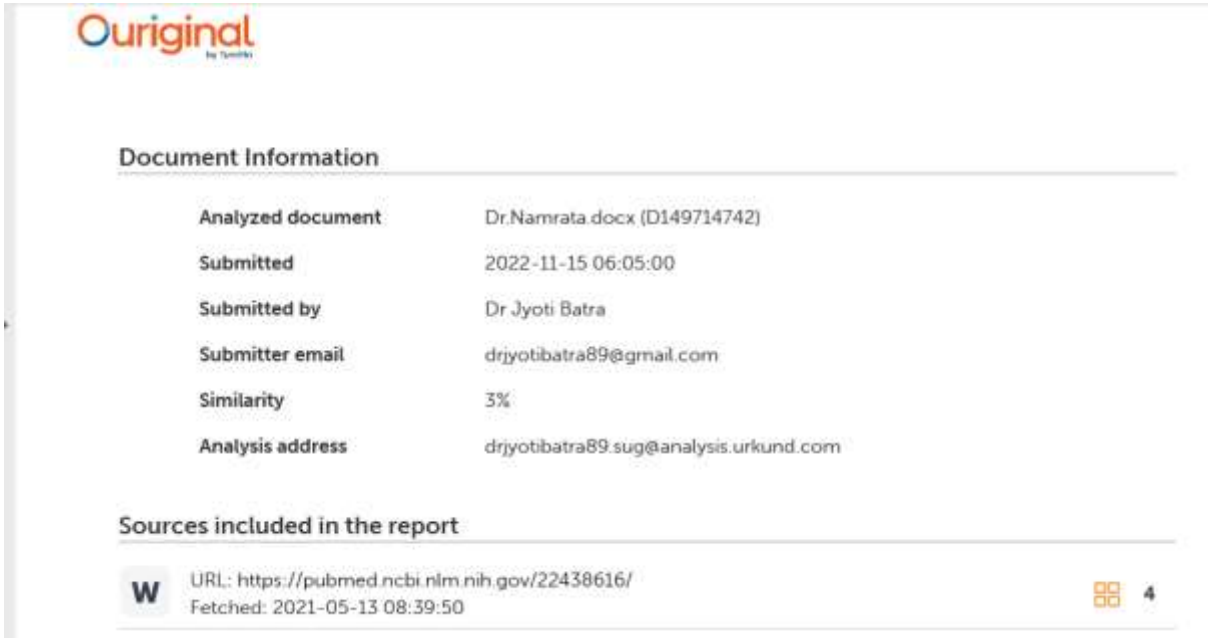
PLAGIARISM CERTIFICATE



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Analysis address	drjyotibatra89.sug@analysis.urkund.com

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STUDY PROFORMA

1) Serial No :
2) Name :
3) Age :
4) Sex :
5) Address :
6) Department :
7) Hospital ID :
8) Chief complaints :
9) Local examination:
10) Other Specific findings:
11) No. of PAP smears received:
12) Lab. No.:
13) PAP smear Report:

CONSENT FORM

I …….. aged..….. Years

R/o …….....……

am willing to participate in study entitled **"ROLE OF PAP SMEAR TO DETECT CYTOLOGICAL ABNORMALITIES IN CERVICAL LESIONS IN A TERTIARY CARE CENTRE**", conducted in the Department of Pathology, Santosh Medical College and Hospital. I am also willing to return for follow up during the course of study. I hereby, give my consent for the participationinthis study.

Signature of Doctor Signature/Thumb impression of patient

Name:

Address:

Phone:

Date:

रोगी का सहमति पत्र

मैं.....उम्र ‥.....साल, ... का / की माता / पिता ;

निवासी.....

.....अपनी स्वेछा से चिकित्सीय अध्ययन में अपने पुत्र / पुत्री को सम्मिलित करने की सहमति प्रदान करता / करती हूं। मुझे सेवा प्रदान करने वाले चिकित्सक ने संतुष्टि की सीमा तक इस चिकित्सीय अध्ययन की प्रकृति व उद्देश्य भली भांति अवगत करा दिया है। मैं समय पर अपने पुत्र / पुत्री कि जांच के लिए सहमति देता / देती हूं।

चिकित्सक के हस्ताक्षर।

रोगी के माता/पिता के हस्ताक्षर

अथवा अंगूठे का निशान

नाम :

पता :

फ़ोन क्रमांक :

दिनांक :

STATISTICAL ANALYSIS

Statistical software used: SPSS 24 version was used for the analysis of the data.

Statistical test applied:

Descriptive statistics like mean, percentage and standard deviation were used.

Chi-Square test of significance was used.

The results were expressed in the form of bar diagrams, pie

charts and pictographs and compared with other similar

studies done in the past as well as with newer studies

KEY TO MASTERCHART

B/L – Bilateral

F – Female

NA – Not available

RT. - Right

MASTERCHART.xlsx